REMARKS

Applicants note with appreciation the Examiner's statements in the Office Action mailed from the US PTO on August 28, 2006 (hereinafter referred to as the "Action") that the claim rejections under 35 U.S.C. 112 and 35 U.S.C. 102 have been overcome. The remaining issue concerns a rejection of the Claims under 35 U.S.C. 103.

Current Amended Claim

Applicants note that the Action addressed the claims as were pending prior to the previous Amendment filed June 1, 2006. For example, the Action states that "[t]he claims recite the treatment of infantile Pomp disease wherein at least 10 mg/kg body weight per week of human acid α-glucosidase are administered to a patient which survives at least to one year of age" (Action, sentence bridging pages 4-5). However, the claims had at that time been amended to set forth different characteristics of the methods of the invention. Nevertheless, this point is now moot because Applicants have cancelled all claims except for Claim 1, which has been slightly amended for the purpose of clarify.

Amended Claim 1 relates to a method of treating a human patient with Pompe's disease, comprising intravenously administering biweekly to the patient a therapeutically effective amount of human acid alpha glucosidase, whereby the concentration of accumulated glycogen in the patient is reduced and/or further accumulation of glycogen is arrested. Applicants will address the Section 103 rejections made by the Examiner in the Action against the previous claims and show why it would not be a legally proper ground of rejection against newly amended Claim 1.

Rejection Under 35 U.S.C. 103

The Examiner rejected the previous claims under 35 U.S.C. 103(a) as being unpatentable over de Barsy *et al.*, Williams *et al.*, and Reuser *et al.*, in view of Bijvoet *et al.* and Van Hove *et al.* Each of the individual references will be discussed below, followed by a discussion of the combination of the references.

De Barsy *et al.*

The de Barsy *et al.* reference (Birth Defects, Original Article Series, Vol. IX, No. 2, pages 184-190 (1973)), describes extraction of enzyme from human placenta and administration of a single dose to an infant. No conspicuous clinical or morphologic improvement was noted after this single dose. Furthermore, de Barsy *et al.* additionally note that no morphologic or biochemical evidence of replacement therapy had been obtained to date, and that it appeared that the enzyme was not being transported to the relevant places in the body. The de Barsy *et al.* reference does not describe treating a human patient with Pompe's disease by administration of an amount of acid alpha-glucosidase in a therapeutically effective dose to the patient. This reference could not be clearer on the point. Note, for example, the statement at the end of the Abstract that "No... clinical improvements were noted...."

Williams *et al.*

The Williams *et al.* reference (Birth Defects, Original Article Series, Vol. XVI, No. 1, pages 415-423 (1980)) describes administration to a patient of two doses of enzyme extracted from human liver and then linked to low density lipoprotein (LDL). Williams *et al.* concluded that their experiments were failures. For example, on page 420, they state that "[a] quadriceps muscle biopsy was performed 2 days after the infusion and the glycogen content was not significantly altered. No α- glucosidase activity against glycogen was detected." They also state that "The slight decrease in glycogen content of tissues is of questionable significance" (p. 422). Thus, like de Barsy *et al.*, Williams *et al.* describe yet another failure in attempting to treat Pompe's disease.

The Examiner states that the de Barsy *et al.* and Williams *et al.* references describe a therapeutic effect, "demonstrated as an increase in enzyme activity in the tissues of infant patients after administration of the enzyme (e.g., de Barsy at page 186, left column; Williams at page 420, second paragraph)" (Action, p. 5, first incomplete paragraph). Applicants note that an increase in enzyme activity is not equivalent to reduction of concentration of accumulated glycogen, or to prevention or arrest of accumulation of glycogen. Further, an increase in enzyme activity is not the therapeutic effect as set forth in the present claim.

Reuser *et al.*

Reuser *et al.* (U.S. 6,118,045) teach transgenic nonhuman animals producing acid alpha glucosidase in milk. Reuser *et al.* do not describe treatment of a human patient, nor do they describe biweekly administration of a therapeutically effective dose to a human patient.

The Examiner emphasizes *in vitro* experiments of Reuser *et al.* in which active enzymes were taken up in fibroblasts from Pompe patients (col. 15, lines 37-65). It is known in the art that *in vitro* cell culture conditions differ significantly from *in vivo* conditions. For example, when enzyme is administered *in vivo* by intravenous infusion, the muscle cells don't come into direct contact with enzyme as they do in cell culture. Furthermore, the endothelial barrier, as well as the interstitial connective tissue, must be passed *in vivo*. See, for example, Reuser *et al.* (*Eur. J. Pediatr.* 161:S106-S111 (2002); a copy of which is attached as Exhibit A) .

The Reuser *et al.* reference does not describe administration of acid alpha-glucosidase to a human being, let alone treatment of a human patient with Pompe's disease.

Bijvoet *et al.*

Bijvoet *et al.* (Biochim. Biophys. Acta 1308:93-96 (1996)) describe production of transgenic recombinant hGAA in mouse milk and the uptake of the enzyme by cultured human fibroblasts. As noted above, *in vitro* uptake by fibroblasts differs significantly from uptake *in vivo*. Like Reuser *et al.*, Bijvoet *et al.* do not describe administration of acid alpha-glucosidase to a human being, let alone treatment of a human patient with Pompe's disease.

Van Hove *et al.*

Van Hove *et al.* describe purification methods for production of recombinant acid alpha-glucosidase produced in Chinese hamster ovary (CHO) cells. Van Hove *et al.* indicate that intravenous injection of enzyme into a guinea pig increased enzyme levels in liver and heart (pp. 613-614). As with Reuser *et al.* and Bijvoet *et al.*, they do not describe administration of acid alpha-glucosidase to a human being, let alone treatment of a human patient with Pompe's disease.

Nonobviousness of Amended Claim 1

With regard to the combination of the references, the Examiner states that "[e]ach of de Barsy, Williams and Reuser suggest the treatment of infantile Pompe's disease by administering human acid α-glucosidase to patients in need thereof" (Action, p. 5, first incomplete paragraph). Applicants disagree and point out that none of these three primary references suggest the treatment of Pompe's disease. de Barsy *et al.* and Williams *et al.* describe attempts to treat Pompe's disease in patients, which failed. Reuser *et al.* describe *in vitro* experiments only.

The deficiencies of the three primary references are not remedied by the addition of the two secondary references. The Examiner combines the three primary references with Bijvoet *et al.* and Van Hove *et al.*, stating *inter alia*:

> [T]he artisan of ordinary skill, recognizing from de Barsy that high dosages would have been reasonably expected to improve the results disclosed therein, would have been motivated to have increased the enzyme dosage to the amounts recited in applicant's claims, suitable quantities of the enzymes being made available by the techniques disclosed in the Reuser, Bijvoet and Van Hove disclosures.

One of ordinary skill in the art would have had no basis for combining the three primary references, as there is no motivation to combine references describing two failed attempts at treatment of patients with a reference describing solely *in vitro* experiments. The only basis for such a combination is impermissible hindsight reconstruction using Applicants' disclosure. Even when combined with hindsight reconstruction, one of ordinary skill in the art would not have obtained the present invention, as the references in combination do not describe treatment of Pompe's disease in a human patient. Furthermore, one of ordinary skill in the art would not have had a reasonable expectation of success given the teachings of de Barsy *et al.*, Williams *et al.* and Reuser *et al.* in view of Bijvoet *et al.* and Van Hove *et al.*, because one would not have known whether administration of enzyme to human individuals would in fact have resulted in therapeutic efficacy.

To establish a reasonable expectation of success for obviousness, there must be "at least some degree of predictability" (see M.P.E.P. 2143.02). Predictability is determined at the time the invention was made: "whether an art is predictable or whether the proposed modification or combination of the prior art has a reasonable expectation of success is determined at the time the invention was made" (see *id.*).

At the time Applicants' invention was made, Pompe's disease had been known for about seventy years, since the early 1930's, and the enzyme deficiency had been known for about forty years, since the 1960's. And yet, attempts at treatment of the disease by administration of replacement enzyme had failed (see, e.g., Van der Ploeg *et al.* (*J. Clin. Invest* 87:513-518 (1991), cited in IDS as reference C14, which lists several references that indicate that attempts at enzyme replacement therapy have failed); Williams *et al.*, discussed previously; and de Barsy *et al.*, also discussed previously). Without treatment, children afflicted with the disease were expected to die, and most infants with the disease weren't expected to live beyond two years of age. It was unknown whether human symptoms could be alleviated by administration of enzyme.

In view of repeated failures known in the art, it is evident that at the time the invention was made, there was a long-felt need but no reasonable expectation of success. As stated in Boehrenger Ingelheim Vetmedica, Inc. v. Schering-Plough Corp., 320 F.3d 1339, 1354, 65 U.S. P.Q. 2d 1961, 1972 (Fed. Cir. 2003), "...there can be little better evidence negating an expectation of success than actual reports of failure."

Applicants' Successful Treatment of Pompe Patients

In this context of the long-felt need for a treatment and the failure of others to treat Pompe's disease successfully, including attempts to treat the disease by enzyme replacement, one skilled in the art would not have had a reasonable expectation of success from the teachings of the references. Nevertheless, Applicants have in fact succeeded in treating patients with Pompe's disease, as evidenced by successful clinical trials that have led to the approval by the Food and Drug Administration of the product, Myozyme®, for the treatment of Pompe's disease. News articles describing the near-miraculous improvement of many Pompe disease patients have appeared: a sampling includes the stories of Megan Assink (ABC News; a copy of the article is attached as Exhibit B); Morgan Borroughs (a copy of the article is attached as Exhibit C); and Sabeel (a copy of the article is attached as Exhibit D).

This incredible success in view of the long-felt need and failures of others renders the claimed invention non-obvious over the teachings of the combination of the five cited references under 35 U.S.C. 103(a).

CONCLUSION

In view of the above amendments and remarks, it is believed that the claim is in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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Date: 2/28/07